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(71) Applicant *(for all designated States except US)*: SUMITOMO PHARMACEUTICALS, K.K. [JP/JP]; 2-8 Doshomachi 2-chome, Chuo-ku, Osaka 541-8510 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MORITA, Shigetoshi [JP/JP]; Kouyou-cho Naka 2-Chome, 1-Ban 214-1322, Higashinada-ku, Koube City 658-0032 (JP). TANAKA, Katsumi [JP/JP]; Tamagawa 1-Chome 9-1 #110, Takatsuki City, Osaka-ku 569-0857 (JP). YOSHIMOTO, Atsushi [JP/JP]; Hukui-cho 12-18, Takarazuka City, Hyougo Prefc. 665-0046 (JP).

(74) Agent: SONODA, Yoshitaka; Sonoda & Kobayashi, 4F/W1, Time-24 Building, 2-45 Aomi, Koto-ku, Tokyo 135-8073 (JP).

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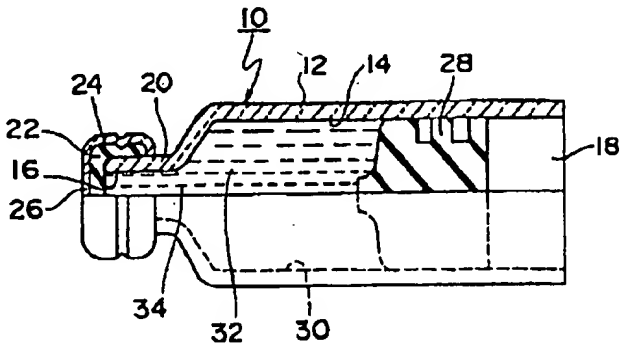
(57) Abstract

The invention has the purpose of offering a storage container wherein flocculation and nebulation of hGH does not occur during storage of an hGH solution. A rubber stopper is formed of rubber such that when one such rubber stopper is immersed in 1ml of a buffer solution having a pH of approximately 5.5 to 6.5 and containing a surfactant, stored while shaking for one week at a temperature of 25 °C, then the metal ion elution rate in the buffer solution is measured using atomic absorption spectrophotometry, the elution rate of polyvalent metal ions is 50 ppm or less.



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Storage Container for Weakly Acidic Solution Formulation Containing Human Growth Hormone, Injection Cartridge Therefor and Storage Method Therefor

TECHNICAL FIELD

The present invention relates to a storage container for a weakly acidic solution formulation containing human growth hormone, an injection cartridge therefor and a storage method therefor.

BACKGROUND ART

Human growth hormone (sometimes referred to as "hGH" below) is a single-chain polypeptide hormone composed of 191 amino acid residues. hGH can undergo decomposition by a number of routes, for example, by deamidation, flocculation, precipitation, oxidation of methionine residues and proteolysis. In order to avoid such decomposition reactions, hGH has conventionally been formulated and sold in freeze-dried form. However, recent years have seen a rising demand for the development of solution formulations for clinical reasons such as in order to improve the compliance of patients by simplifying the method of use, and various such formulations have been announced (see, e.g, PCT Application, Japanese-Language Publication No. Hei 7-809719; Japanese Patent Application, First Publication No. Hei 8-92125).

These solution formulations employ a weakly acidic buffer solution with a pH (pH 6-7) slightly less than the weakly alkaline physiological pH, pH 7-7.5, which has been conventionally employed in freeze-dried formulations. This is because slight alkalinity may cause deamidation of the hGH during storage as a solution. However, with slight acidity of pH 6-7, hGH may tend to precipitate, so that the addition of surfactants has been necessitated for long-term storage. Additionally, the present inventors have observed that even when surfactants are added, precipitation or nebulation of the hGH can occur during long-term storage of the hGH solution depending on the conditions, and the cause of this phenomenon has conventionally been completely unexplained.

On the other hand, since the rubber stoppers or rubber plungers used in injection-type solution formulations are in contact with the solution for a long time in comparison to the case where used in the container of a freeze-dried solution, problems in quality caused by the rubber stopper material can often occur. Whereas examples of problems associated with rubber stoppers include contaminants adhering to the rubber stopper, coring and sticking, a particular problem for solution formulations is the effect of elutes from the rubber stopper on the quality of the pharmaceutical

agent. Rubber stoppers have very complicated properties both chemically and physically, and various types of elute substances from rubber stoppers are known. These are, for example, reported by L. Gramiccioni *et al.* (*Chromatographia*, 28 ('89) 545-550). However, it has yet to be examined which of the elute substances from rubber stoppers have what type of effects on a hGH solution formulation, particularly weakly acidic solution formulations, and there have been no such reports as far as the inventors are aware.

Therefore, the present inventors performed diligent research in this regard, as a result of which they discovered that the formulation container, particularly the material of the rubber stopper is an important factor in the stable storage of hGH solution formulations. That is, they discovered that metal ions dissolve from the rubber stopper during long-term storage and form conjugates with the hGH. Based on this discovery, they found that it is necessary to use a rubber stopper in which the elution of metal ions (especially zinc ions and/or aluminum ions) under certain conditions is below a standard amount in order to prevent degradations of the quality of the hGH solution formulation, thereby arriving at the present invention.

DISCLOSURE OF THE INVENTION

Specifically, the storage container for a weakly acidic solution formulation containing human growth hormone according to the present invention comprises a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; a first sealing member for sealing the first opening; and a second sealing member provided in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with the first sealing member for containing the weakly acidic solution formulation containing human growth hormone. The second sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the

first sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the elution rate of polyvalent metal ions is 20 ppm or less.

A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the polyvalent metal ions are zinc ions or aluminum ions.

An injection cartridge for a weakly acidic solution formulation containing human growth hormone according to the present invention comprises a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; a first sealing member for sealing the first opening, having a thickness such as to be capable of being punctured by a syringe needle; and a second sealing member provided in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with the first sealing member for containing the weakly acidic solution formulation containing human growth hormone. The second sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

An injection cartridge for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the first sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a first sealing member is immersed in 1 ml of a buffer solution

containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A method for storing a weakly acidic solution containing human growth hormone according to the present invention comprises steps of preparing a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; providing a rubber stopper in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming a space with the first sealing member; filling the space with the weakly acidic solution formulation containing human growth hormone; and sealing the first opening with a cap. The rubber stopper is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a rubber stopper is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A method for storing a weakly acidic solution containing human growth hormone according to another mode of the present invention is such that a polyvalent metal ion chelating agent is added to the weakly acidic solution formulation containing a human growth hormone.

The terminology such as "buffer solution containing a surfactant" used in the present specification is defined as follows. "Buffer solution containing a surfactant" refers to a solution containing a citric acid-type, phosphoric acid-type, glycine-type or tris-type buffer, an isotonic agent such as sodium chloride, a surfactant such as Polysorbate 80, Polysorbate 20 or Poloxamer 188, and optionally, other preservatives and the like as needed. Polysorbate 20, Poloxamer 188 and the like are preferred as surfactants.

"Rubber stopper or rubber plunger" refers to a rubber stopper for a syringe vial or a plunger used in a cartridge for a convenience-type syringe formulation. That is, a rubber stopper is a sealing plug composed of rubber used for an antiseptic seal after a vial container is filled with hGH. A rubber plunger is a sealing plug composed of rubber used for an antiseptic seal in an hGH solution-filled cartridge used in hGH administration devices.

"hGH" refers to human growth hormone which was brought into practice almost 20 years ago as a treatment for pituitary dwarfism, of which various medical formulations are commercially available. In the present invention, hGH includes not only hGH proteins from the human pituitary gland (191 amino acids, molecular weight approximately 22,000), but also to human growth hormone equivalents having biologically specific biological activity (e.g. substitution modifications, addition modifications, deletion modifications). Here, biological activity specific to hGH refers mainly to overall growth accelerating activity for causing all human tissues (especially bones) except for the brain to grow mainly during the developmental period, including the effects of accelerating production of bones and cartilage by IGF-I induction, promotion of amino acid intake to cells and protein synthesis, suppression of protein decomposition, promotion of neutral fat metabolism, promotion of sugar metabolism and promotion of electrolyte retention.

"Weakly acidic solution formulation containing hGH" refers to a solution formulation having a buffer with a pH of 5.5-7, and containing hGH as an active ingredient. The appropriate pH range for such an hGH solution formulation is 5.5-7.0, and has been reported to be more advantageously 6.0 (PCT Application, Japanese-Language Publication No. Hei 7-509719).

"Storage container" refers to a fluid storage container such as a vial or cartridge for a syringe as commonly used in the field of pharmaceuticals.

According to the storage container for a weakly acidic solution formulation containing human growth hormone, injection cartridge therefor and storage method therefor of the present invention employing this type of structure, low levels of nebulation preferably, no nebulation is observed in the storage container containing human growth hormone, thus making it possible to offer an hGH solution formulation which is physically and chemically stable.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a side view showing a portion of a storage container according to the present invention in cross-section.

Fig. 2 is a perspective view showing the state of use of the storage container shown in Fig. 1.

BEST MODE FOR CARRYING OUT THE INVENTION

Herebelow, a mode for carrying out the present invention shall be described with reference to the drawings. Fig. 1 shows a storage container according to the present invention. The storage container 10 has a roughly cylindrical container body

12. The container body 12 forms an internal cavity 14, this internal cavity 14 being open at the openings 16, 18 at the ends thereof. In the present embodiment, one end of the container body 12 has a smaller diameter to form a mouth portion 20. The mouth portion 20 has a thin rubber cap 22 and a metallic cap 24 covering this rubber cap 22. As shown in the drawings, these caps 22 and 24 are attached by pressing the cylindrical portion of the metallic cap 24 and the end portion of the tubular portion toward the mouth portion 20 and deforming it. The metallic cap 24 has an opening 26 opposing the opening 16 on roughly the central axis of the container body, such that by passing a needle into this opening 26 and through the rubber cap 22, it is possible to withdraw fluid from the inside.

In the internal cavity 14 of the container body 12, a roughly cylindrical rubber stopper 28 or rubber plunger is inserted from the opening 18 on the other side. The rubber stopper 28 has a slightly larger outer diameter than the inner diameter of the internal cavity 14 of the container body when in a state of withdrawal from the container body 12. Consequently, when the rubber stopper 28 is in a state of insertion into the internal cavity 14 of the container body 14, a continuous seal is formed between the inner wall 30 forming this internal cavity 14 and the outer circumferential surface of the rubber stopper 28, as a result of which an enclosed chamber 32 is formed between the rubber cap 26 and the rubber stopper 28, and a liquid, i.e. human growth hormone solution (weakly acidic solution formulation containing human growth hormone) 34 can be accommodated in this chamber 32.

When sealing human growth hormone solution 34 into the container body 12, the rubber stopper 28 is inserted from the opening 18 with the caps 26 and 28 unattached to the opening 16. Next, human growth hormone solution 34 is injected into the container body 12 from the opening 16. Finally, this opening 16 is covered with the rubber cap 22 and metallic cap 24, and the edge of the tubular portion of the metallic cap 24 is deformed towards the mouth portion 20 to close the seal. Alternatively, the opening 16 is covered with the rubber cap 22 and the metallic cap 24, and the edge of the tubular portion of the metallic cap 24 is deformed towards the mouth portion 20 to close the seal. Next, the human growth hormone solution 34 is injected into the container body 12 through the opening 18. Finally, the rubber stopper 28 is inserted from the opening 18 while compressing to deform.

The human growth hormone solution 34 contained in the storage container 12 having this type of structure is, for example, injected into a patient using the syringe device (administration device) 40 of Fig. 2 offered under the trade name "Pen 100S" from Disetronic. This syringe device 40 is composed of a holder 42 for accommodating

the storage container 10 and an actuator 44 coupled to the rear end of this holder 42. Upon use, the storage container 10 is inserted into the holder 42 and the actuator is fitted to the rear end of this holder 42. Additionally, a cap 46 is attached to the front end of the holder 42. This cap 46 is provided with a needle 48 on an end surface, the two tips of this needle 48 protruding respectively from the inside end surface and outside end surface, the end of the needle 48 protruding from the inner end surface puncturing the rubber cap 22. In this state, the actuator 44 is operated, and the rubber stopper 28 of the storage container 12 is pressed. As a result, the human growth hormone solution 34 inside the storage container is delivered through the needle 48.

Herebelow, the rubber stopper of the storage container 12 shall be explained in detail. There are no restrictions as to the material of the rubber stopper as long as it is a material capable of being used in rubber stoppers for medical purposes. Butyl rubber, butyl chloride rubber and butadiene rubber are known as basic elastomers, and any of these may be used. Additionally, while the rubber stopper (or plunger) is used in combination with a vial and injection cartridge, their material and shape are not particularly restricted. Aside from glass which is commonly used, it is also possible to use, for example, synthetic resins such as polypropylene.

A rubber stopper suitable for the solution storage container of the present invention is most preferably selected by the following experiments.

(1) A buffer solution (pH 6) containing a surfactant is prepared, and 1 ml is put into a glass vial. The above-mentioned solution may optionally include isotonics, stabilizers, preservatives, anti-oxidants, solubilizers and excipients as appropriate. The test conditions may be changed according to the composition, storage conditions and method of use of the hGH solution formulation which is to be used, but in view of the purpose of strictly evaluating the amount of elutes from the rubber stopper, it is undesirable to add agents such as chelating agents which may have an effect on the metal ions.

(2) A single rubber stopper (approximately 1 g) is immersed in the above-described vial, and stored while shaking at 25 °C for one week.

(3) The amount of metal ions which have dissolved into the buffer solution is measured by atomic absorption spectrophotometry.

(4) Rubber stoppers having an elution rate of 50 ppm or less of polyvalent metal ions, particularly zinc and/or aluminum are selected. Preferably, those with an elution rate of zinc and/or aluminum ions of 20 ppm or less per rubber stopper under the above-given conditions are chosen.

(5) If the rubber stopper material fails to reach the above standards, it can be

modified or treated to provide it with properties suitable for the storage container of the present invention by means of surface treatment or the like. For example, by coating the rubber stopper with a fluorine resin laminate, plastic, bulk silicon or other macromolecules by means of commonly known methods, it is possible to prevent the rubber stopper from directly contacting the hGH solution, thereby suppressing the elution of metal ions from the rubber stopper. Rubber stoppers coated by means of such conventional methods should be evaluated by means of the test described in paragraphs (1)-(4), and selected under similar criteria for employment in the container of the present invention.

Unlike a rubber stopper for a vial, a plunger must use a material which is harder (there are usually more additives to the rubber) than that of a simple vial stopper due to the functional property of moving inside the cartridge during use and deciding the dosage delivered. While coatings by bulk silicon or the like which may be scraped off due to friction are not generally held to be preferable for surface treatment, it is possible to have a coating with only a small amount of silicon in order to reduce the friction. Therefore, the plunger which is suitable for carrying out the present invention must clear standards which are more stringent than those of a normal rubber stopper for vials. Specifically, the tests described in paragraphs (1)-(3) should be performed, and those with a zinc and/or aluminum ion concentration of 20 ppm or less should be used.

Herebelow, experiments performed on the rubber stoppers of the storage container shall be explained.

1) Method of Analysis

(i) Metal Ion Content

The quantitative analysis of metal ions in the solution was performed using atomic absorption spectrophotometry according to conventional methods.

(ii) hGH Content, Polymer Content

Size-exclusion chromatography was performed using a TSK G2000SWXL with 200 mM sodium phosphate (pH 6.8)/0.1% SDS/0.04% Polysorbate 20 as the mobile phase. The flow rate was 0.7 mL/min, and measured at 214 nm.

(ii) Deamidate Content

Anion exchange chromatography ((HPIEC) was performed using a TSK DEAE 3SW column (0.75 mm × 7.5 cm) at 40 °C with a flow rate of 1.0 mL/min. This column was equilibrated with a 25 mM bis-tris buffer (pH 5.8). Elution was performed using a 40 min gradient of 25 mM bis-tris buffer/0.5 M sodium chloride. Measurements were performed at 280 nm.

2) Experimental Method

(i) Experiment 1 Effects of Metal Ions on hGH

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. A solution in which was dissolved zinc acetate, aluminum chloride, calcium chloride and magnesium chloride was antiseptically added to the above-described sample so as to make the metal ion concentration a standard concentration, and the changes in the solubility state were observed.

(ii) Experiment 2 Elution of Metal Ions from Rubber Stopper

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. Each rubber stopper (rubber stopper B1 of Company B and rubber stoppers A1, A2, A3 and A4 of Company A) was immersed in the above-described sample, which was then stored at room temperature while shaking for a week. Thereafter, the metal ion concentration in the solution was measured.

(iii) Experiment 3 Effects of Rubber Stopper on hGH

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. A rubber stopper (rubber stopper B1 of Company B) with a high metal ion elution rate was immersed in the above-described sample, and 200 ppm of 2-sodium ethylene diamine 4-acetate was added. The change in the solubilization state was observed after letting stand at room temperature for 1 week.

(iv) Experiment 4 Effects of Various Rubber Stoppers on hGH

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. Each type of rubber stopper was immersed in the hGH solution. The pH change, content change, deamidate content and polymer content were measured after storing the prepared samples for one month under 5 °C and 25 °C conditions.

3) Experiment Results

(i) Experiment 1 Effects of Metal Ions on hGH

With regard to zinc ions and aluminum ions, nebulation was observed in samples wherein 100 ppm and 50 ppm were respectively added. On the other hand, there was no nebulation in the samples into which magnesium ions and calcium ions

were added (Table 1).

Table 1

Metal Ion	Conc. Added	0 ppm	20 ppm	50 ppm	100 ppm
Zn^{2+}	Property pH	clear 6.06	clear	clear 6.00	nebulation 5.97
Al^{3+}	Property pH	clear 6.03	clear	nebulation 5.82	nebulation 5.58
Mg^{2+}	Property pH	clear 6.08	clear	clear	clear
Ca^{2+}	Property pH	clear 6.05	clear	clear	clear

(ii) Experiment 2 Elution of Metal Ions from Rubber Stopper

With the rubber stopper B1 of Company B, the rate of elution of aluminum ions was considerably higher than in other rubber stoppers (Table 2).

Table 2

Rubber Stopper	Zn^{2+}	Al^{3+}	Mg^{2+}	Ca^{2+}
B1	82.7	2.5	0.2	0.0
A1	0.4	0.2	0.4	0.0
A2*	0.3	0.0	0.1	0.0
A3*	17.3	1.5	0.4	0.0
A4*	3.9	1.1	0.1	0.0

Note: elution units: ppm/unit

rubber stoppers weights approximately 850 mg/unit

*rubber stoppers weigh approximately 240 mg/unit

(iii) Experiment 3 Effects of Rubber Stoppers on hGH

The samples in which the rubber stopper B1 of company B were immersed were observed to have nebulation during storage. However, the sample in which a rubber stopper B1 of Company B was immersed after adding the chelating agent 2-sodium ethylene diamine 4-acetate was not observed to have nebulation (Table 3).

Table 3

	No Rubber Stopper	Rubber Stopper Present*
EDTA 0 ppm	clear	nebulation
EDTA 200 ppm	clear	clear

* rubber stopper B1 of Company B

After one week of stationary storage at room temperature

(iv) Experiment 4 Effects of Various Rubber Stoppers on hGH

Nebulation was observed during storage of a sample in which the rubber stopper B1 of Company B was immersed, and a drop in content was confirmed (25 °C for 1 month). Additionally, in the samples in which the rubber stopper B1 of Company B was immersed, the pH of the solution rose and there was considerable generation of deamidates and polymer content.

Table 4

Rubber Stopper	Storage Conditions	pH	Solubility State	hGH Content[1)]	Deamidate Content[2)]	Polymer Content
B1	5 °C for 1M	6.72	clear	100%	2.8%	0.8%
	25 °C for 1M	7.75	nebulation	81%	20.5%	10.4%
A3	5 °C for 1M	6.17	clear	99%	2.8%	0.3%
	25 °C for 1M	6.30	clear	102%	10.7%	1.0%
A4	5 °C for 1M	6.20	clear	99%	3.0%	0.3%
	25 °C for 1M	6.41	clear	101%	11.7%	0.6%
A1	5 °C for 1M	6.15	clear	100%	3.0%	0.2%
	25 °C for 1M	6.21	clear	100%	10.7%	0.5%
None	5 °C for 1M	6.08	clear	100%	3.2%	0.4%

1) The hGH content was calculated with the sample content after storage at 5 °C for 1M without a stopper as 100%.

2) The deamidate content includes cyclic imides.

CLAIMS

1. A storage container for a weakly acidic solution formulation containing human growth hormone, comprising:

a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening;

a first sealing member for sealing said first opening; and

a second sealing member provided in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with said first sealing member for containing the weakly acidic solution formulation containing human growth hormone;

said storage container for a weakly acidic solution formulation containing human growth hormone being characterized in that:

said second sealing member is composed of a type of rubber such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

2. A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein said first sealing member is composed of a type of rubber such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

3. A storage container for a weakly acidic solution formulation in accordance with either claim 1 or 2, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

4. A storage container for a weakly acidic solution formulation in accordance with any one of claims 1-3, wherein said polyvalent metal ions are zinc ions or aluminum ions.

5. An injection cartridge for a weakly acidic solution formulation containing

human growth hormone, comprising:

a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening;

a first sealing member for sealing said first opening, having a thickness such as to be capable of being punctured by a syringe needle; and

a second sealing member provided in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with said first sealing member for containing the weakly acidic solution formulation containing human growth hormone;

said injection cartridge for a weakly acidic solution formulation containing human growth hormone being characterized in that:

said second sealing member is composed of a type of rubber such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

6. An injection cartridge for a weakly acidic solution formulation containing human growth hormone in accordance with claim 5, wherein said first sealing member is composed of a type of rubber such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

7. A method for storing a weakly acidic solution containing human growth hormone, comprising steps of:

preparing a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening;

providing a rubber stopper in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming a space with said first sealing member;

filling said space with the weakly acidic solution formulation containing human growth hormone; and

sealing said first opening with a cap;

said method for storing a weakly acidic solution containing human growth hormone being characterized in that said rubber stopper is composed of a type of rubber such that after such a rubber stopper is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

8. A method for storing a weakly acidic solution containing human growth hormone in accordance with claim 7, comprising a step of adding a polyvalent metal ion chelating agent to the weakly acidic solution containing human growth hormone.

9. A sealing member for a storage container for a weakly acidic solution formulation, the sealing member comprising:

a type of rubber such that after the sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

10. The sealing member of claim 9 wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

11. The sealing member of claim 9 wherein said polyvalent metal ions are zinc ions or aluminum ions.

12. A process for determining whether a sealing member is suitable for use in a storage container for a weakly acidic solution formulation containing human growth hormone, the process comprising the steps of:

(a) immersing the sealing member in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5;

(b) storing the immersed sealing member at a temperature of 25 °C for 1 week;

(c) simultaneously with step (b) shaking the immersed sealing member at a temperature of 25 °C for 1 week; and

(d) measuring the elution rate of polyvalent metal ions in said buffer

solution.

13. The process of claim 12 wherein step (d) is performed by atomic absorption spectrophotometry.

14. The process of claim 12 further comprising a step (e) of determining that the sealing member is suitable if the elution rate measured in step (d) is 50 ppm or less.

15. The process of claim 12 further comprising a step (e) of determining that the sealing member is suitable if the elution rate measured in step (d) is 20 ppm or less.

16. The process of claim 12 further comprising a step (e) of adding a polyvalent metal ion chelating agent to the weakly acidic solution containing human growth hormone.

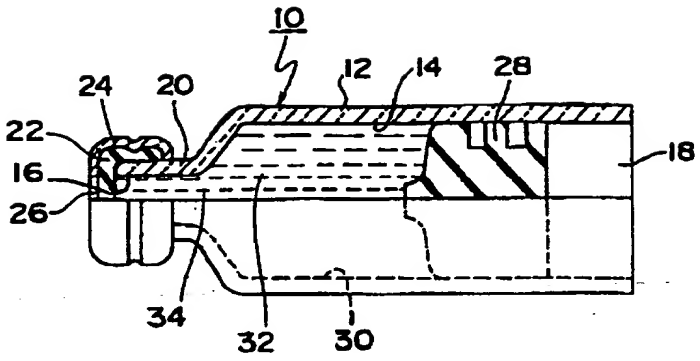

FIG. 1

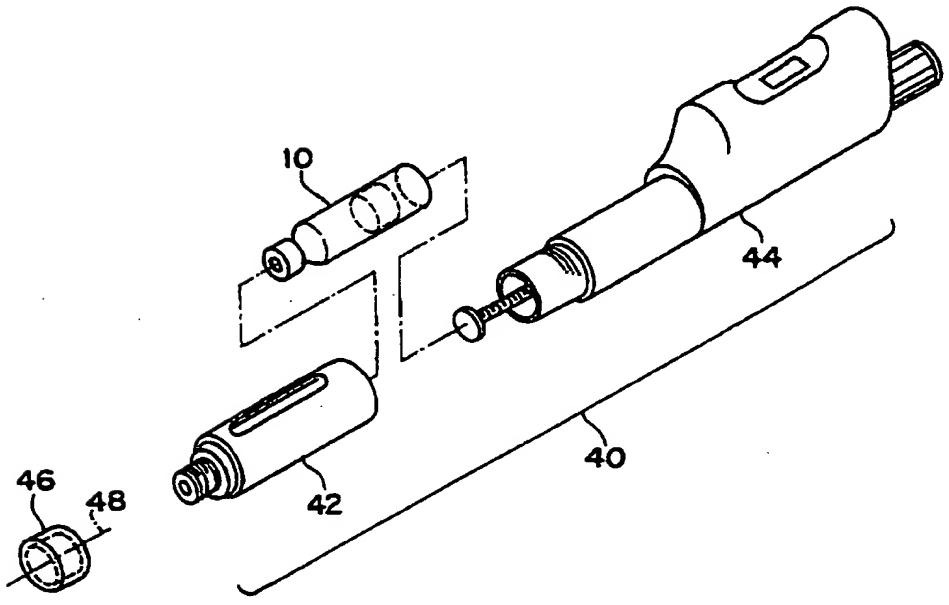

FIG. 2

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/[redacted] 00/00608

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/315

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B65D A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 977 027 A (SCHWABE KARL D) 11 December 1990 (1990-12-11) column 1, line 21 - line 32 claims 1,2,6-9	1-3,5,6, 9,10
A		4,7,11

X	EP 0 148 426 A (WIMMER PHARMA GUMMI GMBH) 17 July 1985 (1985-07-17) abstract; claim 1; figure 12	1-3,5,6, 9,10
A		4,7,11

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2000	12/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sedy, R

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 199317 Derwent Publications Ltd., London, GB; Class A12, AN 1993-140154 XP002146187 -& JP 05 077846 A (POLYTECH DESIGN KK), 30 March 1993 (1993-03-30) abstract	1,5,9
A	DATABASE WPI Section Ch, Week 199624 Derwent Publications Ltd., London, GB; Class B04, AN 1996-235992 XP002146188 -& JP 08 092125 A (NIPPON CHEM RES KK), 9 April 1996 (1996-04-09) cited in the application abstract	7,12
A	US 5 064 083 A (ALEXANDER BARBARA ET AL) 12 November 1991 (1991-11-12) abstract	1

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 00 /00608

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11 (all in part)

Present claims 1-11 relate to a method or apparatus defined by reference to a desirable characteristic or property, namely the second sealing member of the storage container is composed of a type of a rubber such that the envisaged elution rate of polyvalent metal ions in a buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

The claims cover all methods and apparatus having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methodsor apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method or apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods or apparatus comprising a storage container and a rubber stopper coated with a fluorine resin laminate, plastic, bulk silikon or other macromolecules (see description page 8, lines 2-4).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inte[illegible] Application No
PCT/[illegible]00/00608

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4977027 A	11-12-1990	DE 3727626 A	02-03-1989
		AU 608885 B	18-04-1991
		AU 2105688 A	23-02-1989
		DK 464888 A	20-02-1989
		EP 0303984 A	22-02-1989
		IL 87481 A	08-07-1993
		JP 1070056 A	15-03-1989
		JP 1816341 C	18-01-1994
		JP 5023786 B	05-04-1993
		PT 88292 A	30-06-1989
		ZA 8806088 A	26-04-1989
EP 0148426 A	17-07-1985	DE 3346351 A	11-07-1985
		AT 47697 T	15-11-1989
		DE 3480334 D	07-12-1989
		EP 0210667 A	04-02-1987
JP 5077846 A	30-03-1993	NONE	
JP 8092125 A	09-04-1996	NONE	
US 5064083 A	12-11-1991	CA 2034868 A	09-09-1991

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 11669.2WO01

Box No. I TITLE OF INVENTION

STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SUMITOMO PHARMACEUTICALS, K.K.
2-8 Doshomachi 2-chome
Chuo-ku
Osaka 541-8510
Japan

☐ This person is also inventor

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MORITA, Shigetoshi
Kouyou-cho Naka 2-Chome 1-Ban 214-1322
Higashinada-ku
Koube City 658-0032
Japan

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SONODA, Yoshitaka
SONODA & KOBAYASHI
4F/W1, Time-24 Building
2-45 Aomi, Koto-ku
Tokyo 135-8073 Japan

Telephone No. 81-3-5531-5218

Facsimile No. 81-3-5531-5219

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TANAKA, Katsumi
Tamagawa 1-Chome 9-1 #110
Takatsuki City
Osaka-hu 569-0857
Japan

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: JP

State *(i.e. country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YOSHIMOTO, Atsushi
Hukui-cho 12-18
Takarazuka City
Hyougo Prefc. 665-0046
Japan

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: JP

State *(i.e. country)* of residence: JP

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except he United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except he United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒	**AE**	United Arab Emirates	☒	**KZ**	Kazakstan
☒	**AG**	Antigua and Barbuda	☒	**LC**	Saint Lucia
☒	**AL**	Albania	☒	**LK**	Sri Lanka
☒	**AM**	Armenia	☒	**LR**	Liberia
☒	**AT**	Austria and utility model	☒	**LS**	Lesotho
☒	**AU**	Australia	☒	**LT**	Lithuania
☒	**AZ**	Azerbaijan	☒	**LU**	Luxembourg
☒	**BA**	Bosnia and Herzegovina	☒	**LV**	Latvia
☒	**BB**	Barbados	☒	**MD**	Republic of Moldova
☒	**BG**	Bulgaria	☒	**MG**	Madagascar
☒	**BR**	Brazil	☒	**MK**	The former Yugoslav Republic of Macedonia
☒	**BY**	Belarus	☒	**MN**	Mongolia
☒	**CA**	Canada	☒	**MW**	Malawi
☒	**CH and LI**	Switzerland and Liechtenstein	☒	**MX**	Mexico
☒	**CN**	China	☒	**MA**	Morocco
☒	**CR**	Costa Rica	☒	**NO**	Norway
☒	**CU**	Cuba	☒	**NZ**	New Zealand
☒	**CZ**	Czech Republic and utility model	☒	**PL**	Poland
☒	**DE**	Germany and utility model	☒	**PT**	Portugal
☒	**DK**	Denmark and utility model	☒	**RO**	Romania
☒	**DM**	Dominica	☒	**RU**	Russian Federation
☒	**DZ**	Algeria	☒	**SD**	Sudan
☒	**EE**	Estonia and utility model	☒	**SE**	Sweden
☒	**ES**	Spain	☒	**SG**	Singapore
☒	**FI**	Finland and utility model	☒	**SI**	Slovenia
☒	**GB**	United Kingdom	☒	**SK**	Slovakia and utility model
☒	**GD**	Grenada	☒	**SL**	Sierra Leone
☒	**GE**	Georgia	☒	**TJ**	Tajikistan
☒	**GH**	Ghana.	☒	**TZ**	Tanzania
☒	**GM**	Gambia	☒	**TM**	Turkmenistan
☒	**HR**	Croatia	☒	**TR**	Turkey
☒	**HU**	Hungary	☒	**TT**	Trinidad and Tobago
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☒	**IL**	Israel	☒	**US**	United States of America
☒	**IS**	Iceland	☒	**UZ**	Uzbekistan
☐	**JP**	Japan	☒	**VN**	Viet Nam
☒	**KE**	Kenya	☒	**YU**	Yugoslavia
☒	**KG**	Kyrgyzstan	☒	**ZA**	South Africa
☒	**KP**	Democratic People's Republic of Korea	☒	**ZW**	Zimbabwe
☒	**KR**	Republic of Korea and utility model			

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 02 April 1999 (02.04.1999)	Hei 11-96,443	JP		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which the earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*
ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year):* Number: Country (or regional Office):

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	4
description (excluding sequence listing part)	:	11
claims	:	4
abstract	:	1
drawings	:	1
sequence listing part of description	:	
Total number of sheets	:	21

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) *identified in Box No VI as item(s):*
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ Other *(specify): Gen. Transmittal (in dupl)*
   Check in the amount of $ 2393.
   Return Postcard

Figure of the drawings which should accompany the abstract: _

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

By _____
Yoshitaka Honoda

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SONODA, Yoshitaka
Sonoda & Kobayashi
4F/W1, Time 24 Building
2-45 Aomi, Koto-ku
Tokyo 135-8073
JAPON

Date of mailing (day/month/year) 22 August 2000 (22.08.00)	
Applicant's or agent's file reference 11669.2WO01	**IMPORTANT NOTIFICATION**
International application No. PCT/IB00/00608	International filing date (day/month/year) 31 March 2000 (31.03.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 02 April 1999 (02.04.99)
Applicant SUMITOMO PHARMACEUTICALS, K.K. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
02 Apri 1999 (02.04.99)	11/096443	JP	28 July 2000 (28.07.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Ingrid Aulich

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SONODA, Yoshitaka
SONODA & Kobayashi
4F/W1 Time 24 Building
2-45 Aomi, Koto-ku
Tokyo 135-8073
JAPON

RECEIVED
'01. 1. -4
SONODA & KOBAYASHI

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	27.12.2000
Applicant's or agent's file reference: 11669.2WO01	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/00608	31/03/2000	02/04/1999

International Patent Classification (IPC) or both national classification and IPC

A61M5/315

Applicant

SUMITOMO PHARMACEUTICALS, K.K. et al

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☐	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02/08/2001.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Ceccarelli, D

Formalities officer (incl. extension of time limits)

Terzic, K
Telephone No. +49 89 2399 2052

Form PCT/IPEA/408 (cover sheet) (January 1994)

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-16,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-16 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Although apparatus claims 1, 5, and 9 and method claims 7 and 12 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, i.e. overlapping scope, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought or in respect of the terminology used for the features of that subject-matter.
The aforementioned claims therefore lack conciseness.
Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1, 5, 7, 9 and 12 do not meet the requirements of Article 6 PCT.

1.1 **No examination according to Article 33(1) PCT is to be expected before this objection is overcome.**

1.2 In order to overcome this objection, it would appear appropriate to file an amended set of claims defining the relevant subject-matter in terms of **a single independent claim in each category** followed by dependent claims covering features which are merely optional (Rule 6.4 PCT).

2. The applicant is requested to file new claims which take account of the above comments and Article 34(2)(b) PCT.
When filing amended claims the applicant is also invited to consider the comments of the Search Examiner in the International Search Report and should also be aware of the fact that problems with unity of invention (Rule 13 PCT) may arise.
The new independent claims to be filed must be clearly novel and involve an inventive step over the documents cited in the Search Report.
The applicant should also indicate in the letter of reply the difference of the

subject-matter of the new independent claim vis-à-vis the state of the art and the significance thereof.

3. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

   If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

Re Item VII
Certain defects in the international application

1. The following documents should be cited in the description since they represent the state of the art in the field of the application (Rule 5.1(a)(ii) PCT):

   D1: US-A-4 977 027 (SCHWABE KARL D) 11 December 1990 (1990-12-11)
   D2: EP-A-0 148 426 (WIMMER PHARMA GUMMI GMBH) 17 July 1985 (1985-07-17)
   D3: US-A-5 064 083 (ALEXANDER BARBARA ET AL) 12 November 1991 (1991-11-12)

2. The claims do not contain any reference signs to the figures, which would be appropriate to facilitate the understanding of the claims themselves (Rule 6.2(b) PCT).

3. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims, Rule 5.1(a)(iii) PCT. Care should be taken during revision, especially on the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 34(2)(b) PCT).

D

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
11669.2WO01		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/00608	31/03/2000	02/04/1999
International Patent Classification (IPC) or national classification and IPC A61M5/315		
Applicant SUMITOMO PHARMACEUTICALS, K.K. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/11/2000	22.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ceccarelli, D Telephone No. +49 89 2399 2653

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/00608

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-11 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-16.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-16 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Although apparatus claims 1, 5, and 9 and method claims 7 and 12 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, i.e. overlapping scope, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought or in respect of the terminology used for the features of that subject-matter.
The aforementioned claims therefore **lack conciseness**.
Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1, 5, 7, 9 and 12 do not meet the requirements of Article 6 PCT and no meaningful examination according to Article 33(1) PCT could be carried out.

Re Item VII

Certain defects in the international application

1. The following documents should have been cited in the description since they represent the state of the art in the field of the application (Rule 5.1(a)(ii) PCT):

   D1: US-A-4 977 027 (SCHWABE KARL D) 11 December 1990 (1990-12-11)
   D2: EP-A-0 148 426 (WIMMER PHARMAGUMMI GMBH) 17 July 1985 (1985-07-17)
   D3: US-A-5 064 083 (ALEXANDER BARBARA ET AL) 12 November 1991 (1991-11-12)

2. The claims do not contain any reference signs to the figures, which would be appropriate to facilitate the understanding of the claims themselves (Rule 6.2(b) PCT).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 November 2000 (30.11.00)	
International application No. PCT/IB00/00608	**Applicant's or agent's file reference** 11669.2WO01
International filing date (day/month/year) 31 March 2000 (31.03.00)	**Priority date** (day/month/year) 02 April 1999 (02.04.99)
Applicant MORITA, Shigetoshi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

01 November 2000 (01.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

Int. Jonal Application No
PCT/IB 00/00608

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/315

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B65D A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 977 027 A (SCHWABE KARL D) 11 December 1990 (1990-12-11) column 1, line 21 - line 32 claims 1,2,6-9	1-3,5,6, 9,10
A	---	4,7,11
X	EP 0 148 426 A (WIMMER PHARMA GUMMI GMBH) 17 July 1985 (1985-07-17) abstract; claim 1; figure 12	1-3,5,6, 9,10
A	---	4,7,11
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2000	12/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sedy, R

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intl ional Application No
PCT/IB 00/00608

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 199317 Derwent Publications Ltd., London, GB; Class A12, AN 1993-140154 XP002146187 -& JP 05 077846 A (POLYTECH DESIGN KK), 30 March 1993 (1993-03-30) abstract ---	1,5,9
A	DATABASE WPI Section Ch, Week 199624 Derwent Publications Ltd., London, GB; Class B04, AN 1996-235992 XP002146188 -& JP 08 092125 A (NIPPON CHEM RES KK), 9 April 1996 (1996-04-09) cited in the application abstract ---	7,12
A	US 5 064 083 A (ALEXANDER BARBARA ET AL) 12 November 1991 (1991-11-12) abstract -----	1

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 00 /00608

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11 (all in part)

Present claims 1-11 relate to a method or apparatus defined by reference to a desirable characteristic or property, namely the second sealing member of the storage container is composed of a type of a rubber such that the envisaged elution rate of polyvalent metal ions in a buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

The claims cover all methods and apparatus having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methodsor apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method or apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods or apparatus comprising a storage container and a rubber stopper coated with a fluorine resin laminate, plastic, bulk silikon or other macromolecules (see description page 8, lines 2-4).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IB 00/00608

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4977027 A	11-12-1990	DE 3727626 A	02-03-1989
		AU 608885 B	18-04-1991
		AU 2105688 A	23-02-1989
		DK 464888 A	20-02-1989
		EP 0303984 A	22-02-1989
		IL 87481 A	08-07-1993
		JP 1070056 A	15-03-1989
		JP 1816341 C	18-01-1994
		JP 5023786 B	05-04-1993
		PT 88292 A	30-06-1989
		ZA 8806088 A	26-04-1989
EP 0148426 A	17-07-1985	DE 3346351 A	11-07-1985
		AT 47697 T	15-11-1989
		DE 3480334 D	07-12-1989
		EP 0210667 A	04-02-1987
JP 5077846 A	30-03-1993	NONE	
JP 8092125 A	09-04-1996	NONE	
US 5064083 A	12-11-1991	CA 2034868 A	09-09-1991

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
11669.2W001		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 00/00608	31/03/2000	02/04/1999
Applicant		
SUMITOMO PHARMACEUTICALS, K.K.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11 (all in part)

Present claims 1-11 relate to a method or apparatus defined by reference to a desirable characteristic or property, namely the second sealing member of the storage container is composed of a type of a rubber such that the envisaged elution rate of polyvalent metal ions in a buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

The claims cover all methods and apparatus having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methodsor apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method or apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods or apparatus comprising a storage container and a rubber stopper coated with a fluorine resin laminate, plastic, bulk silikon or other macromolecules (see description page 8, lines 2-4).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]B 00/00608

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/315

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B65D A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 977 027 A (SCHWABE KARL D) 11 December 1990 (1990-12-11) column 1, line 21 - line 32 claims 1,2,6-9	1-3,5,6, 9,10
A		4,7,11

X	EP 0 148 426 A (WIMMER PHARMA GUMMI GMBH) 17 July 1985 (1985-07-17) abstract; claim 1; figure 12	1-3,5,6, 9,10
A		4,7,11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2000	12/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sedy, R

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 199317 Derwent Publications Ltd., London, GB; Class A12, AN 1993-140154 XP002146187 -& JP 05 077846 A (POLYTECH DESIGN KK), 30 March 1993 (1993-03-30) abstract	1,5,9
A	DATABASE WPI Section Ch, Week 199624 Derwent Publications Ltd., London, GB; Class B04, AN 1996-235992 XP002146188 -& JP 08 092125 A (NIPPON CHEM RES KK), 9 April 1996 (1996-04-09) cited in the application abstract	7,12
A	US 5 064 083 A (ALEXANDER BARBARA ET AL) 12 November 1991 (1991-11-12) abstract	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00608

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JP 8092125 A	09-04-1996	NONE	
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